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(57) Abstract

The early administration of Lactobacillus GG during the rehydrating phase is capable of shortening the duration of the diarrhoea, preventing the following food allergy syndrome in the patient, and promoting a faster weight increase. To this purpose there is provided a preparation to be administered by mouth and formed of an oral rehydrating solution (ORS) of the commercial type, such as Dicodral 60, in which an effective amount of both alive and inactivated ferments Lactobacillus GG is contained.

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Treatment of the acute infant's diarrhoea and prevention of allergic reactions to foods swallowed in the following phase by administering Lactobacillus GG in the oral rehydrating solution

The present invention relates to the treatment of acute infant's diarrhoea and more particularly the early use of the bacterium Lactobacillus GG during the rehydrating phase with the purpose of reducing the duration of the diarrhoea, preventing food allergy syndromes in the patient, and promoting a faster weight recovery.

Acute diarrhoea due in most cases to intestinal infections (gastroenteritis) acquired by orofecal way is still a very important sanitary problem. In fact, 2 to 3 billions of cases of acute diarrhoea occur yearly in the world, such cases causing an estimated mortality of about 5 million infants aged up to five.

In Italy and West Europe the mortality due to gastroenteritis has gone progressively and considerably down in recent years and is reduced to 1-10 cases over 100,000 infants/year today. However, also under such circumstances, acute diarrhoea is an event of great importance considering that it is very frequent (recent epidemiological studies in Scandinavia and in Italy show that each infant has, as an average, a little more than one episode/year of acute diarrhoea). Therefore, direct cost for the treatment and indirect cost due to the absence of the mothers from work are huge. It should not be forgotten that in 4-6% of the cases an acute diarrhoea lasts more than 14 days, thus exposing the infant to the

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real risk of developing malnutrition or acquiring food allergies (which actually take place in a large number of cases), thus inducing further complications and, in the best case, excluding some foods for very long time.

As can be seen from the foregoing, it should be very useful to have therapeutical means capable of reducing the duration of the diarrhoetic symptomatology, blocking effectively the possible evolution regarding the food allergy, and improving at the same time the digestion-absorption conditions in order to promote the weight recovery of the little patients.

The present invention seeks to provide a formulation responsive to such requirements.

The current therapy of gastroenteritis is addressed to an unquestionable physiopathologic approach: administering an oral rehydrating solution (ORS) based on a mixture of electrolytes and glucose formulated according to precise requirements so as to promote the intestinal absorption of water and mineral salts and to restore the hydro-electrolytic wealth endangered by diarrhoea. Such an approach, which has been made possible by the knowledge of the physiopathology of the intestinal absorption-digestion processes and has been widely used for the last 10-15 years also in the adult's diarrhoea, has certainly contributed to save many human lives and cannot be questioned at all. However, as well known, it takes no effect on the symptoms, the diarrhoea persisting unchanged, and then is only partially responsive to the above-mentioned requirements.

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It is also known that apart from some specific substances the etiologic therapy of the gastroenteritis cannot be carried out as only some bacterial enteric pathogens may be eradicated by a specific therapy accompanied by a shortening of the symptomatology.

In recent years it has been proved (Raza et al., 1995) that a milk enzyme, Lactobacillus casei subspecies rhamnosius (so-called also Lactobacillus GG initially isolated from the intestinal bacterial flora of a man), administered both in the form of powder and yoghurt produced by the fermentation of the milk with said enzyme, is capable of shortening by about 2 days the duration of the diarrhoea in little patients with gastroenteritis by rotavirus which is considered as the most common etiologic agent of acute infant's diarrhoea in the world. It has been also proved that the administering of such an enzyme has no side-effects at all and is accompanied by an increase of the immunity to rotavirus.

Furthermore, it has been thereafter proved that the same product is also capable of thoroughly preventing the increase of the intestinal permeability of the rats caused by the early administering of milk proteins of different species to the growing animals. The latter result is of great importance: it is well known that during an infectious gastroenteritis (that by rotavirus is really the most studied condition) the permeability of the intestinal mucosa is altered by the damage induced by the intestinal infectious process. That such a condition predisposes to the entrance of heterologous food macromolecules and then is capable to initiate a food allergy syndrome in susceptible subjects is an

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incontrovertible proof. In fact, it is well supported with documentary evidence that a considerable amount of the allergies to cow's milk afflicting about 3% of the infants came into being after a gastroenteritis.

Starting from such remarks it is assumed that the early administering of Lactobacillus GG during the rehydration phase (i.e. the initial acute diarrhoea treatment phase in which the oral rehydrating solution (ORS) is administered without other foods) can not only further reduce the duration of the diarrhoea (allowing a better and earlier contact of the agent with the damaged intestinal mucosa) but also allow the allergy to food (especially proteins of cow's milk) administered in the following phase to be prevented.

The result of an experimentation carried out on a sample of several little patients proved that a preparation to be administered by mouth and formed of the ferment Lactobacillus GG in a rehydrating solution, identified as the commercial preparation Dicodral 60, in an amount of 100,000 to 1,000,000,000 C.F.U. (Colony Forming Unit) every 500 ml solution, prevents food allergy syndromes besides strongly influencing the duration of the diarrhoea, and allows the weight to be faster recovered.

The effectiveness of administering the above-mentioned preparation is self-evident from the results of the experimentation shown in Tables 1 and 2.

Children aged one to twelve having 4 evacuations/day of liquid faeces for one to some days but not more than 5 days were subjected to test. Criteria for the exclusion

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from the test were: preceding treatment with antidiarrhoea products, syndrome of short intestine, associated renal or hepatic diseases, paralytic ileum, chronic inflammatory intestine diseases (Crohn disease, ulcerous rectocolitis). The test was conducted according to a double-blind method controlled by placebo. The enlisted patients were randomly assigned either to group A assuming Lactobacillus GG (added to the oral rehydrating solution (ORS) Dicodral 60: 10,000,000 C.F.U./250 ml ORS) or to group B assuming placebo (only Dicodral 60). All patients were rehydrated with said solutions for 6-8 hours and then resumed the usual diet still assuming the oral rehydrating solution until the end of diarrhoea. Furthermore, registry, anthropometric, clinic data of each patient was registered as well as a sample of faeces was taken for the analysis of the following enteric pathogens: Rotavirus and Adenovirus of the enteric type (40-41), Giardia and Cryptosporidium, Salmonella, Shigella, Campylobacter, Yersinia, Aeromonas, E. Coli pathogens (ETEC, EPEC, EHEC, EIEC, EAggEC, searched by specific DNA probes). Finally, analysis were carried out on the following parameters which were registered at the beginning and at periodic intervals during the analysis: body weight, defecation (frequency and quality), total duration of diarrhoea, oral feeding and complications such as vomit and intolerance to carbohydrates (the latter searched daily by Clinitest).

RESULTS

Data relates to 32 patients, 17 in group A, 15 in group B. Both groups were comparable in age, weight, and duration of diarrhoea at the admission (table 1). The medium age was 23.9 months (range: 2-61) in group A, 25.2 months

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(range: 3-96) in group B. At the admission diarrhoea was lasting on the average from 2.9 days (range: 1-5) in group A, 2.6 days (range: 1-4) in group B. The mean duration of diarrhoea from the beginning of the treatment was 1.3 days (range 1-3) in group A, and 1.4 days (range 1-3) in group B. The mean duration of diarrhoea from the beginning of the treatment could be estimated in hours for 15 patients: it was 17.1 hours (range: 4-34) in group A, and 27 hours (range: 6-70) in group B (table 2). The mean number of liquid evacuations in the two days of evaluation was 5.6 faecal discharges (range 1-11) in group A and 7.3 faecal discharges (range 1-24) in group B. The mean weight increase was always greater in group A in all of the evaluation days as shown in the diagram. Among the complications, vomit was present in 17.6% of group A and 20% of group B; the intolerance of lactose was present in 5.8% of group A and 6.6% of group B. Finally, among the isolated pathogens, Rotavirus was isolated in 11.76% of group A and 6.6% of group B.

The results of the experiments have to be considered as preliminary, however, they allow as from now some salient points to be pointed out:

Lactobacillus GG administered by mouth in the oral rehydrating solution has proved to be well tolerated and did not result in any intolerance or side effects.

The duration of an acute diarrhoea tends to be shorter in the treated patients than in the controls, especially if the duration is expressed in hours; however, the dispersion of the values and the little number of cases do not allow yet to confirm such a statement according to a statistic validation.

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The most interesting data, however, is the faster weight increase of the infants assuming the ferment than the controls. As the latter data relates to the first 24 hours of observation, it is of course sign of a more effective rehydration and/or re-nourishing. One could then suppose that the treated patients markedly improve their digestion conditions after a few hours administration with the consequence of a faster restoration of the hydro-electrolytic wealth.

Table 1.- Observation Data

	Group A 1-GG (n=17)	Group B Placebo (n=15)	P N.S.
Age (month)	23.9 (2-61)	25.2 (3-96)	N.S.
Weight (g)	11841 ± 6250	13439 ± 6700	N.S.
Undernourished	2 (12%)	2 (13%)	N.S.
No dehydration	7%	7%	N.S.
Dehydration < 5%	93%	93%	N.S.
Dehydration 5-10%	-	14%	N.S.
Dehydration > 10%			N.S.
Duration of the diarrhoea (days)	2.9 ± 0.7	2.6 ± 1.1	N.S.
Rotavirus diarrhoea	2 (11.76%)	1 (6.6%)	N.S.

Table 2.- Clinic Course

	Group A (n=17)	Group B (n=15)
Vomit (%)	3 (17.64%)	3 (20%)
Intolerance to lactose	1 (5.88%)	1 (6.64%)
Duration of diarrhoea from the beginning of the treatment	1.33 days range (1-3)	1.46 days range (1-3)

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	Group A (n=9)	Group B (n=6)
Duration of diarrhoea from the beginning of the treatment	17.1 hours range (4-34)	27 hours range (6-70)

As can be seen, the product of the present invention may then find application in the acute infant's diarrhoea, in the infectious infant's gastroenteritis, in the therapy and prevention of the infant's protracted diarrhoea syndrome as well as in the prevention of the allergy to cow's milk caused by gastroenteritis.

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Claims

1. Use of an effective amount of both alive and inactivated ferments Lactobacillus GG in the oral rehydrating solution (ORS) for the early treatment of the acute infant's diarrhoea of a variety of aetiologies.

2. A preparation to be administered by mouth for the treatment of the acute infant's diarrhoea which is formed of a rehydrating solution (ORS) containing an effective amount of both alive and inactivated Lactobacillus GG.

3. A preparation to be administered by mouth for the treatment of the acute infant's diarrhoea which is formed of a rehydrating solution (ORS) containing an amount of both alive and inactivated Lactobacillus GG between 100,000 and 1,000,000,000 C.F.U. (Colony Forming Units) every 500 ml solution.

4. The preparation to be administered by mouth for the treatment of the acute infant's diarrhoea of the preceding claim, wherein the rehydrating solution (ORS) is identified by the commercial preparation Dicodral 60.

5. A preparation to be administered by mouth for the treatment of the acute infant's diarrhoea of claim 4, wherein the amount of Lactobacillus GG is 10,000,000 C.F.U. every 250 ml Dicodral 60.

6. A preparation to be administered by mouth for the treatment of the acute infant's diarrhoea of claims from 2

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on, wherein it reduces the duration of the diarrhoea, prevents allergies to foods swallowed in the following phase, and allows a faster weight increase.

7. A method for the treatment of acute infant's diarrhoea, the prevention of allergies to foods swallowed in the following phase and a faster weight increase, wherein there is provided the early administration of Lactobacillus GG in the initial phase of treatment of the acute diarrhoea by adding it to the oral rehydrating solution (ORS).

M. Ketelaars

Van: M. Ketelaars
Verzonden: maandag 7 juni 2004 12:15
Aan: 'Algra, T.'
Onderwerp: RE: octrooi aanvraag

Beste Theo,

Op alle drie je vragen kan ik bevestigend antwoorden.
T.a.v. het kostenplaatje dien je wel rekening te houden met de omzetting van de PCT aanvrage na 30 maanden!

Met vriendelijke groet,
Maarten F.J.M. Ketelaars

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beste Maarten

Ik vindt vandaag jullie offerte in de post, na een weekje vakantie.
Ik heb daarover nog even een paar vragen.

1)

Als ik het goed begrijp is het kostenplaatje voor het NLR als volgt en uitsluitend:

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Klopt dit?

2)

Ik neem aan dat wij in onze opdracht ons eerst kunnen beperken tot punten a en b en dat we later nog beslissen of we c ook doen.

3)

Lopen alle betalingen via jullie bureau?

vr gr

Theo

Dr Ir Theo Algra
National Aerospace Laboratory NLR

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